

## General

### Guideline Title

Management of narcolepsy in adults.

### Bibliographic Source(s)

Billiard M, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, Sonka K. Management of narcolepsy in adults. In: Gillhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 513-28. [118 references]

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, Pollmacher T, Reading P, Sonka K, EFNS Task Force. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006 Oct;13(10):1035-48.

## Recommendations

### Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Points [GPP]) are defined at the end of the "Major Recommendations" field.

#### Excessive Daytime Sleepiness and Irresistible Episodes of Sleep

The first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep is not unequivocal. In cases when the most disturbing symptom is excessive daytime sleepiness, modafinil should be prescribed based on its efficacy, limited adverse effects, and easiness of manipulation. Modafinil can be taken in variable doses from 100 to 400 mg/day, given in one dose in the morning or two doses, one in the morning and one early in the afternoon. However, it is possible to tailor the schedule and dose of administration according to the individual needs of the patient. On the other hand, when excessive daytime somnolence coexists with cataplexy and poor sleep, sodium oxybate may be prescribed, based on its well-evidenced efficacy on the three symptoms. However, this benefit should be balanced with its more delicate manipulation: the dose should be carefully titrated up to an adequate level over several weeks; the drug should not be used in association with other sedatives, respiratory depressants and muscle relaxants; vigilance should be held for the possible development of sleep-disordered breathing; and depressed patients should not be treated with this drug. Sodium oxybate should be given at a starting dose of 4.5 g/night, increasing by increments of 1.5 g at 4-week intervals. Adverse effects may require to reduce the dose and titrate more slowly. The optimal response on excessive daytime sleepiness may take as long as 8 to 12 weeks. Supplementation with modafinil is generally more successful than sodium oxybate alone. Methylphenidate may be an option in case modafinil is insufficiently active and sodium oxybate is not recommended. Moreover, the short-acting

effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Methylphenidate LP and mazindol may be of interest in a limited number of cases.

Behavioral treatment measures are always advisable. Essentially the studies available support on a B Level the recommendation to have regular nocturnal sleep times and to take planned naps during the day, as naps temporarily decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.

### Cataplexy

Based on several Class I evidence (Level A rating) studies, first-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Adverse effects may need the dose to be reduced and titrated more slowly. Most patients will start to feel better within the first few days, but the optimal response at any given dose may take as long as 8 to 12 weeks. The drug should not be used in association with other sedatives, respiratory depressants, and muscle relaxants; vigilance should be held for the possible development of sleep-disordered breathing; and depressed patients should not be treated with the drug. Second-line pharmacological treatments are antidepressants. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are the most potent anticataplectic drugs. However, they have the drawback of anticholinergic adverse effects. The starting dosage should always be as low as possible. Selective serotonin re-uptake inhibitors (SSRIs) are slightly less active but have fewer adverse effects. The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used today but lacks any published clinical evidence of efficacy. The norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the well-evidenced efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy.

### Hallucinations and Sleep Paralysis

Recommendations are as for cataplexy.

### Poor Sleep

According to recent studies with sodium oxybate, this agent appears as the most appropriate to treat poor sleep (Level A). Benzodiazepines or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (Level C). Unfortunately, objective evidence is lacking over intermediate or long-term follow-up. The improvement in poor sleep reported by some patients once established on modafinil is noteworthy.

### Parasomnias

Based on the available information it is difficult to provide guidance for prescribing in parasomnias associated with narcolepsy other than to recommend conventional medications.

### Associated Features

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) should be treated no differently in narcoleptic patients than the general population, although it has been shown that continuous positive airway pressure (CPAP) does not improve excessive daytime sleepiness in most narcolepsy subjects. There is usually no need to treat periodic limb movements in sleep (PLMS) in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (Level C) as in non-narcoleptic depressed patients.

### Psychosocial Support and Counselling

Interaction with narcoleptic patients and counseling from trained social workers are recommended (Level C).

### Good Practice Points

A prerequisite before implementing a potentially lifelong treatment is to establish an accurate diagnosis of narcolepsy with or without cataplexy, and to check for possible comorbidity. Following a complete interview the patient should undergo an all-night polysomnography followed immediately by a multiple sleep latency test (MSLT). Human leucocyte antigen (HLA) typing is rarely helpful. Cerebrospinal fluid (CSF) hypocretin-1 measurement may be of help and is added as diagnostic test in the revised International Classification of Sleep Disorders, particularly if the MSLT cannot be used or provides conflicting information. Levels of CSF hypocretin are only significantly reduced or absent in cases of narcolepsy with cataplexy. In the absence of cataplexy, the value of measuring hypocretin is debatable.

Once diagnosed, patients must be given as much information as possible about their condition (the nature of the disorder, genetic implications, medications available and their potential adverse effects) to help them cope with a potentially debilitating condition.

Regular follow-up is essential to monitor response to treatment, adapt the treatment in case of insufficient response or adverse effects, and above

all encourage the patient to persist with a management plan. Another polysomnographic evaluation of patients should be considered in case of worsening of symptoms or development of other symptoms, but not for evaluating treatment in general.

#### Definitions:

#### Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
- c. Exclusion/inclusion criteria are clearly defined
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

#### Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points Where there was a lack of evidence but consensus was clear, the task force has stated their opinion as Good Practice Points.

## Clinical Algorithm(s)

None provided

## Scope

### Disease/Condition(s)

Narcolepsy

### Guideline Category

Management

Treatment

### Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pharmacology

Sleep Medicine

## Intended Users

Physicians

Social Workers

## Guideline Objective(s)

To reach a consensus on the use of modafinil and sodium oxybate and other available medications for the treatment of narcolepsy

## Target Population

Adult patients suffering from narcolepsy with and without cataplexy

## Interventions and Practices Considered

1. Complete interview, all-night polysomnography, multiple sleep latency test (MSLT), cerebrospinal fluid hypocretin-1 measurement
2. Patient education about the condition, available medications, and potential side effects
3. Pharmacological treatment
  - Excessive daytime sleepiness and irresistible episodes of sleep: modafinil, sodium oxybate, methylphenidate, amphetamines, behavioral treatment
  - Cataplexy, hallucinations and sleep paralysis: sodium oxybate, antidepressants, avoidance of triggers
  - Poor sleep: benzodiazepines or non-benzodiazepine hypnotics, sodium oxybate, modafinil
  - Parasomnia: conventional medications
  - Treatment of features associated with narcolepsy
4. Psychosocial support and counselling

## Major Outcomes Considered

- Effectiveness of treatment in terms of reduced daytime sleepiness, irresistible episodes of sleep, and cataplectic attacks; increased sleep latencies; improved sleep efficiency and overall sleep quality
- Adverse effects of medications
- Features associated with narcolepsy (obstructive sleep apnoea/hypopnoea syndrome, periodic limb movements in sleep, depression)

## Methodology

### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The best available evidence to address each question was sought, with the classification scheme by type of study design according to the European Federation of Neurological Societies (EFNS) guidance document. If the highest level of evidence was not sufficient or required updating, the literature search was extended to the lower adjacent level of evidence. Several databases were used including Cochrane Library, Medline, EMBASE, and Clinical Trials until September 2005. Previous guidelines for treatment were sought. Each member of the task force was assigned a special task, primarily based on symptoms of narcolepsy (excessive daytime sleepiness and irresistible episodes of sleep, cataplexy, hallucinations and sleep paralysis, disturbed nocturnal sleep, parasomnias) and also on associated features (obstructive sleep apnoea hypopnoea syndrome, periodic limb movements during sleep, neuropsychiatric symptoms) and special treatments (behavioural and experimental).

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
- c. Exclusion/inclusion criteria are clearly defined
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

## Methods Used to Analyze the Evidence

Systematic Review

## Description of the Methods Used to Analyze the Evidence

Not stated

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Each member of the Task Force was first invited to send his own contribution to the chairman. A meeting gathering seven of the nine members of the task force was then scheduled during the 5th International Symposium on Narcolepsy in Ascona, Switzerland, October 10–15, 2004. A draft of the guidelines was then prepared by the chairman and circulated amongst all members of the Task Force for comments. On receipt of these comments the chairman prepared the final version that was circulated again amongst members for endorsement.

The current revision of the European Federation of Neurological Societies (EFNS) guidelines was prepared by the chairman based on the same databases until November 2009 and circulated among members for endorsement.

## Rating Scheme for the Strength of the Recommendations

### Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points Where there was a lack of evidence but consensus was clear, the task force has stated their opinion as Good Practice Points.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

### Peer Review

## Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate management of narcolepsy

## Potential Harms

- *Modafinil* is associated with headache (13%), nervousness (8%), and nausea (5%). Most adverse effects are mild to moderate in nature. On rare occasions worsening of cataplexy has been observed.
- The main adverse effects of *amphetamines* are minor irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia, and insomnia, but doses of over 120% of the maximum recommended by the American Academy of Sleep Medicine are responsible for a significantly higher occurrence of psychosis, substance misuse, and psychiatric hospitalizations.
- Adverse effects of *methylphenidate* are the same as with amphetamines. However methylphenidate probably has a better therapeutic index than dextroamphetamine with less reduction of appetite or increase in blood pressure. Tolerance may develop.
- Adverse effects of *sodium oxybate* at doses ranging from 3 to 9 g nightly are dose-related and include adverse effects were dose-related and included dizziness in 23.5% to 34.3%, nausea in 5.9% to 34.3%, headache in 8.8% to 31.4%, confusion in 3.0% to 14.3%, enuresis in 0 to 14.3%, and vomiting in 0 to 11.4% of the cases. Of concern is the abuse potential of sodium oxybate/gamma-hydroxybutyrate (GHB). Also of concern are the reports implicating sodium oxybate with several cases of worsening sleep-related breathing disturbances or even death.
- Adverse effects of *mazindol* include dry mouth, nervousness, constipation, and less frequently nausea, vomiting, headache, dizziness, tachycardia and excessive sweating. Rare cases of pulmonary hypertension and cardiac valvular regurgitation have been reported. For this reason, it has been withdrawn from the market in several countries. Its use in narcolepsy is still warranted according to most experts, but as a third-line treatment and with close monitoring. Tolerance is uncommon, and abuse potential may be low.
- The use of *selegiline* is limited by potentially sympathomimetic adverse effects and interaction with other drugs.
- *Clomipramine* is associated with anticholinergic effects including dry mouth, sweating, constipation, tachycardia, weight increase, hypotension, difficulty in urinating, and impotence. Patients may experience with tricyclics a worsening or 'de novo' onset of rapid eye movement (REM) sleep behaviour disorder. Moreover, there is a risk, if the tricyclics are suddenly withdrawn, of a marked increase in number and severity of cataplectic attacks, a situation referred to as 'rebound cataplexy', or even 'status cataplecticus'. Tolerance to the effects of tricyclics may develop. The newborns of mothers submitted to longstanding treatment with high doses of antidepressants may show symptoms of atropine intoxication. Thus, if cataplexy is mild, it is advisable to cease the anti-cataplectic drug before conception.
- Adverse effects of *selective serotonin re-uptake inhibitors (SSRI)* are less pronounced than with tricyclics. They include central nervous system excitation, gastrointestinal upset, movement disorders and sexual difficulties. The risk of marked increase in number and severity of cataplectic attacks has been documented after discontinuation of SSRIs.
- Minor side effects of norepinephrine reuptake inhibitors are dry mouth, hyperhidrosis, constipation, and restlessness.
- Atomoxetine has been shown to slightly but significantly increase heart rate and blood pressure in large samples. Thus caution is needed.

Refer to the original guideline document for more information on adverse effects of these and other drugs.

## Contraindications

### Contraindications

- Dextroamphetamine, with a U.S. Food and Drug Administration (FDA) category D classification, and methamphetamine, with an FDA category C classification, are contraindicated during conception and pregnancy.
- Use of methylphenidate is contraindicated in pregnancy
- Modafinil, sodium oxybate, and selective serotonin reuptake inhibitors (SSRIs) are not recommended during pregnancy.
- Mazindol is classified as FDA category B without controlled studies in humans. It is contraindicated in pregnant women.
- Co-administration of triptans and serotonin specific reuptake inhibitors is contraindicated.
- Selegiline is another FDA category B drug without controlled studies in humans. It is contraindicated in pregnant women.

## Qualifying Statements

### Qualifying Statements

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best

available evidence. It is not intended to have legally binding implications in individual cases.

- The recommendations expressed in these guidelines are based on the best currently available knowledge. However, developments in the field of narcolepsy are rapidly advancing and the use of new symptomatic treatments and of treatments directed at replacing hypocretin or even preventing the loss of neurons containing the neuropeptide may become a reality in the near future.

## Implementation of the Guideline

### Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Billard M, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G, Sonka K. Management of narcolepsy in adults. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 513-28. [118 references]

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2006 Oct (revised 2011)

## Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

## Source(s) of Funding

European Federation of Neurological Societies

## Guideline Committee

European Federation of Neurological Societies Task Force on Management of Narcolepsy in Adults

## Composition of Group That Authored the Guideline

*Task Force Members:* M. Billiard, University of Montpellier, France; Y. Dauvilliers, Gui de Chauliac Hospital, Montpellier, France; L. Dolenc-Grošelj, University Medical Center, Ljubljana, Slovenia; G.J. Lammers, Leiden University Medical Center, The Netherlands; G. Mayer, Department of Neurology, Schwalnstadt-Treysa, Germany; K. Sonka, Charles University, Prague, Czech Republic

## Financial Disclosures/Conflicts of Interest

Dr Billiard was a member of the Xyrem (UCB Pharma) advisory board and received honoraria from UCB for invited talks.

Dr Dauvilliers was involved in a clinical trial with Cephalon and another one with Orphan. He is a member of the Xyrem (UCB Pharma) advisory board and has recently received honoraria from Cephalon.

Dr Dolenc-Grošelj received honoraria from Medis (the Slovenian representative for Xyrem) for invited talks.

Dr Lammers is a member of the Xyrem (UCB Pharma) advisory board and has received honoraria from UCB for invited talks.

Dr Mayer received honoraria from Cephalon and UCB Pharma for invited talks. He was involved in one trial with Cephalon and two trials with Orphan Drugs. He is a member of the Xyrem advisory board.

Dr Sonka was involved in two trials with Orphan and is currently involved in a trial with Cephalon. Dr Sonka is also a member of the Xyrem advisory board.

## Guideline Status

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This guideline updates a previous version: Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Grošelj L, Lammers GJ, Mayer G, Pollmacher T, Reading P, Sonka K, EFNS Task Force. EFNS guidelines on management of narcolepsy. *Eur J Neurol* 2006 Oct;13(10):1035-48.

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies \(EFNS\) Web site](#)

## Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI on April 11, 2007. The information was verified by the guideline developer on May 25, 2007. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Provigil (modafinil) Tablets. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This NGC summary was updated by ECRI Institute on February, 20, 2012. This summary was updated by ECRI Institute on December 20, 2012 following the U.S. Food and Drug Administration advisory on Xyrem (sodium oxybate). This summary was updated by ECRI Institute on April 7, 2014 following the U.S. Food and Drug Administration advisory on Methylphenidate ADHD Medications.

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